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(54) Title: TOPICAL TREATMENT FOR INSECT PESTS IN COMPANION ANIMALS

(57) Abstract: The invention provides single-dose topical formulations for controlling an ectoparasite infestation on a companion animal for a prolonged time comprising a spinosyn, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier. It also provides methods for controlling such infestations for a prolonged time comprising topically administering these formulations to the animal.

TOPICAL TREATMENT FOR INSECT PESTS IN COMPANION ANIMALS

Companion animals, including but not limited to dogs, cats, and horses, are an increasingly important part of today's society. They provide pleasure and companionship to human friends, which leads to what has been termed the human-animal bond. Unfortunately, a number of insect pests and parasites can infest or infect these animals. Such pests include, for example, fleas, lice, mosquitoes, mites, ticks and certain fly species. Safe, effective ways to eliminate these pests are desired, both for the animal's well-being and for the comfort of its human associate.

The most common ectoparasites of cats and dogs world-wide are the cat and dog fleas, *Ctenocephalides felis felis* and *Ctenocephalides canis*, respectively. Interestingly, the cat flea very commonly infests dogs. Fleas annoy the animal it infests and the pet's owner. Frequently, fleas cause more serious problems by inducing flea-allergy dermatitis. It has been estimated that flea-related diseases account for over 50% of the dermatological cases reported to veterinarians [D. E. Bevier-Tournay, "Flea and Flea Control" *Curr. Vet. Therapy* **10**: 586-592 (1989)]. In addition, the cat flea is known to transmit tapeworms in dogs and has been implicated in the transmission of cat scratch disease and murine typhus. Other pests of companion animals, such as ticks and mosquitoes, are also known to transmit disease. For example, ticks are known to transmit bacterial and viral diseases; and mosquitoes can infect dogs and cats with the filarial nematode that causes heartworm disease.

Furthermore, economic expenses involved in flea control are high. In the United States, for example, pet owners spend over $1 billion dollars for flea control products annually [R. Conniff, "When It Comes to Pesky Flea, Ignorance is Bliss," *Smithsonian*: **26**: 76-85 (1995)].

Treatments currently available achieve varying degrees of success. Most treatments involve chemicals applied to indoor and outdoor surfaces, as well as to the pet. The chemicals used include a variety of carbamates, organophosphates, pyrethrins and pyrethroids. These compounds often have toxic side effects that are a problem for both the pet and its owner. For example, concentrated forms of pyrethroids available for use on dogs are extremely toxic and lethal to cats and thus cannot and should not be used on cats. In addition, there is evidence that the use of these chemicals has led to multiple category insecticide resistance [N. K. Rust and M. W. Dryden, *Ann. Rev. Entomol.* **42**: 451-473 (1997)]. Thus, there continues to be a need for relatively safe, effective agents for controlling ectoparasites on companion animals, such as cat and dog fleas.

The spinosyns (also known as A83453 factors) are agricultural insecticides that have shown activity against southern armyworm and other insects in the order *Lepidoptera* and cotton aphid and other members of the order *Homoptera*. . (See, for example, U.S. Patent No. 5,571,901).

The spinosyns were also reported to have some ectoparasiticidal activity, i.e., *in vitro* activity against mosquito larvae, black blowfly larvae and adult stable flies , which are members of the insect order *Diptera*, and transient systemic activity against larval blowfly and adult stable fly in guinea pigs and sheep (see U.S. Patent No. 5,571,901, Col. 26-32). Although it was suggested that the spinosyns would be active against a number of ectoparasites in a number of animals by a variety of routes, there have been no subsequent reported studies to support these suggestions.

This invention came about by the discovery that spinosyns, such as spinosyn A, can provide prolonged residual control of an ectoparasite infestation on

companion animals when a single dose of a spinosyn is applied topically to the animal. Thus, the invention provides a method for prolonged control of the ectoparasite in a safer manner than that achieved with previously known treatments.

One aspect of this invention is a long-acting, single-dose topical formulation for controlling an ectoparasite infestation on a companion animal, said formulation comprising an ectoparasiticidal amount of a spinosyn, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier, in topical dosage form.

In another aspect, the invention relates to the use of a single, long-acting topical formulation of a spinosyn, or a physiologically acceptable derivative or salt thereof, for controlling an ectoparasite infestation on a companion animal.

This invention also relates to a method of controlling an ectoparasite infestation on a companion animal for a prolonged time, comprising topically administering a single dose of an effective amount of a spinosyn, or a physiologically acceptable derivative or salt thereof, to the animal. An especially useful method of this invention is a method for controlling a cat or dog flea infestation on a companion animal for a prolonged time comprising topically administering a single dose of an effective amount of a spinosyn, or a physiologically acceptable derivative or salt thereof, to the animal.

The invention further relates to an article of manufacture, comprising packaging material and a formulation for controlling an ectoparasite infestation on a companion animal contained within said packaging material, wherein said formulation comprises

a long-acting topical unit dose of a formulation of this invention, i.e., an ectoparasiticidal amount of a spinosyn, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier; and

wherein said packaging material comprises a label or package insert with instructions for topically administering the dose to the animal.

This article of manufacture, or kit, is particularly appropriate when the companion animal is a dog or a cat. The label or package insert will indicate the number of unit doses to be applied to the dog or cat and the timing of such administration. The timing of doses will generally be every 30 days. The contents of each kit would typically be sufficient to control the ectoparasite infestation for a period of several months.

The invention also relates to the use of a spinosyn, or a physiologically acceptable derivative or salt thereof, for the manufacture of a long-acting single-dose topical medicament for controlling an ectoparasite infestation on a companion animal.

Spinosyns are naturally derived fermentation products. They are macrolides produced by cultivation of *Saccharopolyspora spinosa*. The fermentation produces many factors, including spinosyn A and spinosyn D (also called A83543A and A8354D). Spinosyn A and spinosyn D are the two spinosyns that are most active as insecticides. A product comprised mainly of these two spinosyns is available commercially under the trade name "spinosad". The major spinosyn factor, spinosyn A, is known to have an excellent human and animal safety and toxicological profile.

Each spinosyn has a 12-membered macrocyclic ring that is part of an unusual tetracyclic ring system to which two different sugars are attached, the amino-

sugar forosamine and the neutral sugar 2N,3N,4N-(tri-O-methyl)rhamnose. This unique structure sets the spinosyns apart from other macrocyclic compounds.

Spinosyn A was the first spinosyn isolated and identified from the fermentation broth of *Saccharopolyspora spinosa*. Subsequent examination of the fermentation broth revealed that *S. spinosa* produced a number of spinosyns that have been called spinosyns A to J (A83543A to J). The primary components are spinosyns A and D. Additional spinosyns, lettered from K to W, have been identified from mutant strains of *S. spinosa*. The various spinosyns are characterized by differences in the substitution patterns on the amino group of the forosamine, at selected sites on the tetracyclic ring system and on the 2N,3N,4N-(tri-O-methyl)rhamnose group.

The term "spinosyn or a derivative thereof" as used herein refers to an individual spinosyn factor (spinosyn A, B, C, D, E, F, G, H, J, K, L, M, N, O, P, Q, R, S, T, U, V, W or Y), an N-demethyl derivative of an individual spinosyn factor, or a combination thereof. For convenience, the term "spinosyn component" will also be used herein to mean an individual spinosyn, or a physiologically acceptable derivative or salt thereof, or a combination thereof.

Boeck et al. described spinosyns A-H and J (which they called A83543 factors A, B, C, D, E, F, G, H and J), and salts thereof, in U.S. Patent Nos. 5,362,634 (issued Nov. 8, 1994); 5,496,932 (issued March 5, 1996); and 5,571,901 (issued Nov. 5, 1996). Mynderse et al. described spinosyns L-N (which they called A83543 factors L, M and N), their N-demethyl derivatives, and salts thereof, in U.S. Patent No. 5,202,242 (issued Apr. 13, 1993); and Turner et al. described spinosyns Q-T (which they called A83543 factors Q, R, S and T), their N-demethyl derivatives, and salts thereof, in U.S. Patent Nos. 5,591,606 (issued January 7, 1997) and 5,631,155

(issued May 29, 1997). Spinosyns K, O, P, U, V, W and Y are described, for example, by Carl V. DeAmicis, James E. Dripps, Chris J. Hatton and Laura I. Karr in American Chemical Society's Symposium Series: Phytochemicals for Pest Control, Chapter 11, "Physical and Biological Properties of Spinosyns: Novel Macrolide Pest-Control Agents from Fermentation", pages 146-154 (1997).

The spinosyns can react to form salts that are also useful in the methods and formulations of this invention. The salts are prepared using standard procedures for salt preparation. For example, spinosyn A can be neutralized with an appropriate acid to form an acid addition salt. The acid addition salts of spinosyns are particularly useful. Representative suitable acid addition salts include salts formed by reaction with either an organic or inorganic acid such as, for example, sulfuric, hydrochloric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, cholic, pamoic, mucic, glutamic, camphoric, glutaric, glycolic, phthalic, tartaric, formic, lauric, stearic, salicylic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic and like acids.

The formulations of this invention may further include, in combination with the spinosyn component, one or more other compounds that have activity against the specific ectoparasite or endoparasite to be controlled, such as, for example, synthetic pyrethroids, natural pyrethins, organophosphates, organochlorines, carbamates, foramidines, avermectins, milbemycins, insect growth regulators (including chitin synthesis inhibitors, juvenile hormone analogs, and juvenile hormones), nitromethylenes, pyridines and pyrazoles.

The methods and formulations of this invention have several advantages. First, the spinosyns are naturally derived fermentation products, and

spinosyn A has excellent human and animal safety profile, in contrast to the profiles of the currently used synthetic organically derived compounds, such as synthetic pyrethroids or permethrins, organophosphates, organochlorines, and carbamates. For example, some of the currently used products such as pyrethroids are very toxic to cats and can be lethal.

Another advantage is that spinosyns are very effective against fleas, mites, ticks, lice and flies with post-treatment residual protection, depending upon the dosages used. Furthermore, spinosyns have no cross resistance to compounds currently used to treat these insects. Thus, spinosyns can be used on companion animals against insect populations that have existing levels of resistance to currently used products. Spinosyns can be used, therefore, in integrated pest management (IPM) programs to extend the lifeline of commonly used products where resistance is not developed or has not yet developed.

All ratios, percentages, and parts discussed herein are "by weight" unless otherwise specified.

The term "topical formulation" means a formulation that is suitable to be applied to the external surface of the animal so the ectoparasites will be exposed to lethal levels of the spinosyn component of the formulation. The external surface consists of epidermis, dermis, hair, skin secretions and oils, and skin appendages of the animal. Topical application to the external surface of the animal can be diffuse, as in a spray, dip or dust, or localized as in a pour-on or concentrated as in a spot-on. Topical formulations can be applied on any part of the animal's body, but are typically applied on the head, neck or dorsal midline of the body.

The spinosyn component or components, either alone or in combination with one or more of the other types of compounds listed *supra*, can be formulated into a number of topically applied end-use products or formulations (topical dosage forms). These products or formulations include, but are not limited to, spot-ons, pour-ons, sprays, dips, dusts, lotions, gels, ointments, salves, dressings, ready-to-use towels or towelettes, face masks, cremes, sticks, soaps, shampoos, mousses, collars, medallions, and tail bands. Another example of a topical dosage form is a "tag" that contains a sustained-release formulation with diffusion holes or openings that afford contact with the external surface of the animal

The term "single-dose formulation" or "single-dose medicament" refers to a one time application of a sufficient amount of the formulation to control the ectoparasite infestation.

The term "controlling an ectoparasite infestation" refers to preventing, minimizing or eliminating an infestation by an ectoparasite. The term "ectoparasite" refers to insect or acarine insect pests that commonly infest or infect companion animals. Examples of such ectoparasites include the egg, larval, pupal, nymphal and adult stages of fleas, lice, mosquitoes, mites, ticks and blood-sucking, biting or nuisance fly species.

The term "companion animals" includes dogs, cats, horses, rabbits and other pets owned and maintained in close association with humans as part of the human-animal bond.

The term "prolonged time" comprises a period of at least 7 days, preferably a period of at least two weeks. The term "long-acting" means the activity lasts for a prolonged time.

The methods of this invention are carried out by topically administering the spinosyn component to the animal. As discussed *supra*, topical application may be carried out in a number of ways known in the art. Especially useful methods of topically applying the spinosyn component are spot-ons, sprays and pour-ons. Spot-on treatments are ones in which the active agent is applied once as a single spot in an area that is not accesible to the animal's mouth. In cats and dogs, for example, the area at the base of the neck between the shoulder blades is suitable for spot-on administration. When the spinosyn component is applied as a pour-on, spray, dip, dust, or lotion, it is important to apply a sufficient amount to wet the animal's hair so that the spinosyn component reaches the skin.

In carrying out a method of this invention, an effective amount of a spinosyn or a physiologically acceptable derivative or salt thereof, is applied topically to the companion animal. The terms "effective amount" and "ectoparasiticidal amount" refer to the amount needed to control the particular ectoparasite infestation. As those in the art will understand, this amount will vary depending upon a number of factors. These factors include, for example, the type of companion animal being treated, its weight and its general physical condition and the type of ectoparasite to be controlled.

In general, an effective amount is from 1 to 100 mg of the spinosyn per kg of body weight of the companion animal. More commonly, the effective amount is from 10 to 50 mg/kg of body weight of the animal. In spot-on formulations the spinosyn component will typically comprise from 10 to 60 percent by weight of the formulation.

The following examples illustrate the methods of this invention:

EXAMPLE 1

Prolonged Topical Control of Cat Fleas in Dogs

Dogs of the beagle breed were separated into 5 groups, with two dogs in each group. The dogs were housed indoors. Unfed adult cat fleas (200) were applied to each dog pre-treatment (to assess therapeutic knock-down efficacy) and again at 7, 14, 21 and 28 days post-treatment (to assess post-treatment residual efficacy). Each dog was sprayed once on day 0 with a total volume of 53 mL per dose of a spinosad spray solution. The spray solutions were prepared by making a concentrated solution of spinosad in isopropyl myristate (IPM). The IPM solutions were diluted in water to the desired concentration. One group received only diluted vehicle (control) spray; the remaining 4 groups received a diluted spray solution containing 1, 10, 100 or 1000 ppm spinosad prepared from 0.0429, 0.430, 4.307 and 44.07 mg/mL IPM concentrates, respectively. On days 1 and 7 post-treatment, the dogs sprayed with 100 and 1000-ppm spray solutions showed more than 90% control of the fleas. At days 14 and 21 post-treatment, the dogs treated with the 1000-ppm spray solution showed more than 90% control of the fleas. At day 28 post-treatment, the dogs receiving the 1000-ppm spray solution continued to show about 89% control of the fleas. No adverse reactions were seen or reported during the study with any of the dogs.

EXAMPLE 2

Efficacy of Spinosad in Spot-on and Spray Formulations for the Treatment of *Ctenocephalides felis* on Dogs

In this study dogs of the beagle breed were divided into two control and five treatment groups (3 dogs per group). Each group was infested with fleas as described in Example 1. The treatments were applied either as a spot-on or a spray. Spot-on treatments were applied once as a single spot (1 to 4 mL total volume) placed onto the skin/hair at the base of the neck between the shoulder blades. Spray treatments were administered to cover the entire animal, wetting the hair down to the skin. For spot-on application, spinosad was dissolved in IPM; for spray application, an IPM solution of spinosad was diluted in water to the desired concentration. Two control groups (one housed inside and one housed outside) were treated spot-on with vehicle only. The treatment groups were treated with different doses of spinosad and handled as follows:

Treatment Group	Amount of Spinosad	Application Method	Housed
T1	8 mg/kg	spot-on	Inside
T2	50 mg/kg	spot-on	Inside
T3	8 mg/kg	spot-on	Outside
T4	50 mg/kg	spot-on	Outside
T5	1000 ppm	spray	Inside

The dogs were observed at days 1, 7, 14, 21, 28 and 35. The results observed with the different treatment groups are summarized in **Table 1**.

Table 1: Percent Reduction in Adult Flea Counts in Dogs Treated with Spinosad Compared to Untreated Control Group

Treatment Group	Day Observed					
	1	7	14	21	28	35
T1	98.9	91.9	76.6	67.3	37.5	0
T2	100	99.8	99.8	97.9	92.4	84.7
T3	99.5	93.4	79.1	60.1	16.2	8.6
T4	99.8	100	98.2	97.2	87.3	83.4
T5	100	97.6	80.4	64	54.5	12.9

No adverse reactions were seen.

EXAMPLE 3

Efficacy of Spinosad in Spot-on Formulations for the Treatment of *Ctenocephalides felis* on Dogs

In this study dogs were experimentally infested with fleas as in Example 1 and separated into groups (3 dogs per group). Spinosad was applied as a spot-on as in Example 2. In two groups, it was administered in an aqueous suspension (45%). In two other groups, it was administered in an IPM concentrate (17%). In the control group vehicle without spinosad was applied. The doses were applied as follows:

Treatment Group	Dosage of Spinosad	Vehicle
1	50 mg/kg	Aqueous suspension
2	75 mg/kg	Aqueous suspension
3	50 mg/kg	IPM
4	75 mg/kg	IPM

The results of this study are summarized in **Table 2**.

Table 2: Percent Reduction in Adult Flea Counts in Dogs Treated with Spinosad Compared to Untreated Control Group

Treatment Group	8 hrs	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35
1	23.1	99.6	99.7	98.6	84.6	67	--
2	92.4	99.6	99.7	100	97.4	95	78.5
3	94	99.6	99.7	100	98.1	97	93.1
4	95.9	100	100	100	99.5	98.2	86.1

No adverse results were seen in this study.

EXAMPLE 4

Efficacy of Spinosad in Spot-on and Spray Formulations for the Treatment of *Ctenocephalides felis* on Cats

In this study, cats were divided into a control and five treatment groups (3 cats per group). Each group was infested with fleas as in Example 1 and treated with either a spot-on or spray formulation. Spot-on and spray treatments were carried out as described in Example 2. Spinosad was formulated in IPM solutions or as an aqueous suspension. The control group was treated with a spot-on with IPM vehicle only. The various treatment groups were:

Treatment Group	Amount of Spinosad	Applied	Vehicle
T1	5 mg/kg	spot-on	IPM solution
T2	30 mg/kg	spot-on	IPM solution
T3	180 mg/kg	spot-on	IPM solution
T4	30 mg/kg	spot-on	aqueous suspension

T5	600 ppm	spray	IPM concentrate diluted in water

The cats were observed after 8 hours and at days 1, 7, 14, 21, 29, 35/36 and 42. The results observed with the different treatment groups are summarized in **Table 3**.

Table 3: Percent Reduction in Adult Flea Counts in Cats Treated with Spinosad Compared to Untreated Control Group

Treatment Group	Days Post-Treatment							
	8 hr.	1	7	14	21	29	35/36	42
T1	91.1	96.4	89.8	43	0	0	0	--
T2	99.8	99.6	99.7	98.5	91.4	58.4	24.7	--
T3	99.2	99.6	99.5	100	98.4	95.1	98.9	99.5
T4	97.1	99.8	98.6	90.2	72.7	51.9	33.4	--
T5	97.5	99.6	99.8	64.9	10.7	29.7	0	--

Treatment Group T3 and the control group were observed for an additional 42 days. The results observed at days 49, 56, 63, 70, 77 and 84 are summarized in **Table 3a.**

Table 3a: Percent Reduction in Adult Flea Counts in Cats Treated with Spinosad Compared to Untreated Control Group

Treatment Group	Days Post-Treatment					
	49	56	63*	70	77	84
T3	98.4	98.9	91.4	95.2	89.2	85.9

* Cats were bathed at this point in the trial.

No adverse reactions were seen in this study.

EXAMPLE 5

Efficacy of Spinosad against Adult Stable Fly *(Stomoxys calcitrans)* and House Fly *(Musca domestica)* Infestations on Horses

Five horses were used in this study with one horse per group. The control group was untreated, and 4 groups were treated with an aqueous suspension of spinosad (25 g/L) that was diluted in water just prior to use and applied as a spray to each horse. Each horse was treated with a pressurized spray apparatus by spraying each diluted spray over the dorsum and each side (barrell) of the body from the shoulders to the hips. Each horse received approximately 120 mL of each diluted spray as follows:

Horse #	Treatment[a]
1	untreated
2	500 ppm spinosad
3	1,000 ppm spinosad
4	5,000 ppm spinosad
5	10,000 ppm spinosad

[a] Spinosad sprays were prepared by diluting a 25 g/L spinosad suspension concentrate in an appropriate amount of water to make up each ppm concentration.

After the applied spray had dried, 6 petri dish cages (3 per side) of unfed stable fly and 6 petri dish cages (3 per side) of house fly, each containing 10 adult flies per dish, were placed under a screened belt that was tied around the animal. The bottom of the petri dishes had a mesh that allowed the stable flies to probe through and obtain a blood meal and the house flies to probe through with their mouth parts with both being exposed to the treated hair and skin. The flies in the petri dishes were exposed to the treated surface of each horse for 20 minutes, after which the

plates were removed and taken to the laboratory to evaluate percent kill at 4, 8 and 24 hours post-exposure. Petri dishes were positioned on and exposed to each treated horse immediately after treatment and again on days 1, 3, 5 and 7 post-treatment to evaluate residual activity.

Results: Stable fly control exceeded 90% on the first day in the 5,000 and 10,000 ppm-treated horses. Stable fly control remained above 80% for the 10,000 ppm-treated horse on day 7. House fly control was generally better than stable fly control. The highest percent control was seen on day 3 post-treatment. No adverse reactions were seen.

CLAIMS

1. A long-acting single-dose topical formulation for controlling an ectoparasite infestation on a companion animal, said formulation comprising an ectoparasiticidal amount of a spinosyn, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier, in topical dosage form.

2. A formulation of Claim 1 wherein the spinosyn is spinosyn A.

3. A formulation of Claim 1 or 2 wherein the ectoparasiticidal amount is from 1 to 100 mg of the spinosyn per kg of body weight of the animal.

4. A formulation of Claim 1 or 2 wherein the spinosyn comprises about 10 to 60 percent by weight of the formulation.

5. A formulation of Claim 1, 2, 3 or 4 wherein the animal is a dog, a cat, a horse, or a rabbit.

6. A formulation of Claim 1, 2, 3, 4 or 5 wherein the ectoparasite is a cat flea, a dog flea, a biting or nuisance fly, a mosquito, a tick or a louse.

7. An article of manufacture, comprising packaging material and a formulation for controlling an ectoparasite infestation on a companion animal contained within said packaging material, wherein said formulation comprises

a long-acting topical unit dose of a formulation of Claim 1, 2, 3, 4, 5 or 6; and

wherein said packaging material comprises a label or package insert with instructions for topically administering the dose to the animal.

8. The use of a formulation of Claim 1, 2, 3, 4, 5 or 6 for topically controlling an ectoparasite infestation on a companion animal.

9. The use of a spinosyn, or a physiologically acceptable derivative or salt thereof, for the manufacture of a long-acting single-dose topical medicament for controlling an ectoparasite infestation on a companion animal.

10. A use of Claim 9 wherein the spinosyn is spinosyn A.

11. A method of controlling an ectoparasite infestation on a companion animal for a prolonged time, comprising topically administering a single dose of an effective amount of a spinosyn, or a physiologically acceptable derivative or salt thereof, to the animal.

12. A method of Claim 11 wherein spinosyn is spinosyn A.

13. A method of Claim 11 or 12 wherein the animal is a dog, a cat, a horse or a rabbit.

14. A method of Claim 11, 12 or 13 wherein the ectoparasite is a cat flea, a dog flea, a biting or nuisance fly, a mosquito, a tick or a louse.

15. A long-acting, single-dose topical formulation of a spinosyn, or a physiologically acceptable derivative or salt thereof, for topically controlling an ectoparasite infestation in a companion animal for a prolonged time substantially as hereinbefore described with reference to any one of the Examples.

AMENDED CLAIMS

[received by the International Bureau on 04 December 2000 (04.12.00); original claims 1-15 replaced by new claims 1-9 (2 pages)]

CLAIMS

1. A topical formulation for controlling an ectoparasite infestation on a companion animal, said formulation comprising 10-60% by weight of spinosyn A, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier, wherein said topical formulation is administered to a companion animal in need of treatment at from 1 to 100 mg of spinosyn A per kg of companion animal body weight once every 7 days to two weeks.

2. A formulation of Claim 1 wherein the animal is a dog, a cat, a horse, or a rabbit.

3. A formulation of Claim 1 wherein the ectoparasite is a cat flea, a dog flea, a biting or nuisance fly, a mosquito, a tick or a louse.

4. An article of manufacture, comprising packaging material and a topical formulation for controlling an ectoparasite infestation on a companion animal contained within said packaging material, wherein said formulation comprises

a unit dose of a formulation of Claim 1, 2 or 3; and

wherein said packaging material comprises a label or package insert with instructions for topically administering the dose to the animal.

5. The use of spinosyn A, or a physiologically acceptable derivative or salt thereof, for the manufacture of a topical medicament comprising 10-60% by weight of spinosyn A for controlling an ectoparasite infestation on a companion animal.

6. A method of controlling an ectoparasite infestation on a companion animal, comprising topically administering a single dose once every 7 days to two weeks of a topical formulation containing from 1 to 100 mg of spinosyn A, or a physiologically acceptable derivative or salt thereof, to the animal.

7. A method of Claim 6 wherein the animal is a dog, a cat, a horse or a rabbit.

8. A method of Claim 6 wherein the ectoparasite is a cat flea, a dog flea, a biting or nuisance fly, a mosquito, a tick or a louse.

9. A topical formulation of spinosyn A, or a physiologically acceptable derivative or salt thereof, for topically controlling an ectoparasite infestation in a companion animal substantially as hereinbefore described with reference to any one of the Examples.

INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/US 00/19556

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N43/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,X	EP 0 968 706 A (LILLY CO ELI) 5 January 2000 (2000-01-05) paragraphs '0002!,'0003!,'0008!-'0010!,'0012!,'0015!, '0017!,'0022!	1-15
X	US 5 767 253 A (HUBER MARY L B ET AL) 16 June 1998 (1998-06-16) column 1 -column 13 column 1, line 31 - line 33 column 22 -column 25	1-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2000	06/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bertrand, F

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INTERNATIONAL SEARCH REPORT

Intern: al Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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